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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/752,533	12/29/2000	Stephen M. Coutts	252312005704	1380

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EXAMINER

LUKTON, DAVID

ART UNIT PAPER NUMBER

1653

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/752,533	Applicant(s) COUTTS ET AL.	
	Examiner David Lukton	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 22-98 is/are pending in the application.
- 4a) Of the above claim(s) 22-63,65,81,82 and 98 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 64,66-80 and 83-97 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date: _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>FILED 1/5/04</u> | 6) <input type="checkbox"/> Other: _____ |

Subsequent to the amendment filed 1/5/04, no claim has been added, amended, or cancelled. Claims 22-98 remain pending. Applicants' election of Group VIII (claims 64, 66-80, 83-97) without traverse is acknowledged. Claims 22-63, 65, 81, 82, 98 are withdrawn from consideration. Claims 64, 66-80, 83-97 are examined in this Office action.

Applicants' arguments filed 1/5/04 have been considered and found persuasive in part.

- the previously imposed prior art rejections are withdrawn.
- with the exception of the obviousness double patenting rejection over claim 2 of U.S. Serial No. 08/769041, the obviousness double patenting rejections are maintained.
- The rejection of claims 22-31 33-35, 37, 39-43, 46-50, 54-63 under 35 U.S.C. 112, first paragraph (new matter) is withdrawn; however, claims 64, 66-77, 79, 83-97 are rejected under this statute.

.

As before, the abbreviation "**VPM**" is used hereinbelow to denote a "valency platform molecule".

The abbreviation "**BAM**" is used hereinbelow to denote a "biologically active molecule".

The abbreviation "**PEG**" is used hereinbelow to denote polyethylene glycol.



Claim 64 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. USP 5,276,013.

This ground of rejection was imposed in the previous Office action.

The response (filed 1/5/04) argues that the claimed invention is not obvious because claim 1 of '013 does not suggest that the VPM should be branched. It is true that claim 1 of '013 does not suggest that the VPM should be branched. However, since claim 1 of USP '013 is silent on the matter of branching, it encompasses both.

Perhaps it can be argued that if claim 1 of the patent were considered in a vacuum, one could not be certain that the claim encompassed the invention that is defined by (instant) claim 64. But it is entirely appropriate to consider the contents of the description (of the invention) in endeavoring to assess that which may be encompassed. In particular, conjugates of the "VPM" depicted at the top of columns 17-18 would be encompassed.

It is clear that the preferred BAM's are polynucleotides; a preferred conjugate is represented by a formula at col 19, lines 1-2 and is made from the "VPM" depicted at the

top of columns 17-18. This conjugate meets all of the limitations of instant claim 64.

The rejection is maintained.



Claim 64 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. USP 6,060,056. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 64 is drawn to a (composition comprising a) conjugate of a VPM and a BAM. Claim 1 of U.S.P. 6060056 is drawn to a conjugate of a VPM and a BAM, wherein the BAM must be an analog molecule of an immunogen. Although the scope of the compounds encompassed by BAM is more limited in the '056 patent than is the case here, there is still overlap between the respective genera. The response (filed 1/5/04) argues that claim 1 of the patent does not recite the term "branching" or "branched", and moreover, imposes specific limitations on the BAM. It is true that the limitations on the BAM in the '056 patent are much narrower than what is recited in instant claim 64. However, instant claim 64 encompasses conjugates in which the BAM can be any biologically active molecule; certainly those recited in claim 64 of the patent would be encompassed. As for the issue of branching, it is true that there is no affirmative recitation of branching in claim 1 of USP '056. However, both branched and unbranched VPM's are encompassed. Furthermore, if one looks at the disclosure of '056 to see what is encompassed, examples of

branched VPM's are disclosed, such as the one at col 13, line 27+.

The rejection is maintained.



Claim 64 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. USP 5552391. Although the conflicting claims are not identical, they are not patentably distinct from each other.

As indicated previously, claim 64 is drawn to a (composition comprising a) conjugate of a VPM and a BAM, wherein the VPM is branched and can contain PEG. For example, the conjugates depicted in figure 6a of the patent fall within the scope of claim 64. The response asserts that the rejection is traversed, but no specific traversal is offered. Accordingly the rejection is maintained without further comment.



Claim 64 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22 and 32 of U.S. Serial No. 09/753350. Although the conflicting claims are not identical, they are not patentably distinct from each other. [This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented].

Claim 22 of 09/753350 is drawn to a conjugate of a VPM and a BAM. The claim specifies that the VPM must be branched. Claim 32 of S.N. 09/753350 contains all of the

limitations of claim 22 (of S.N. 09/753,350), and further requires that the VPM comprises PEG.

Perhaps if claim 22 of S.N. 09/753350 were read in a vacuum, one could not be certain that the claim encompassed the invention that is defined by (instant) claim 64. But it is entirely appropriate to consider the contents of the description (of the invention) in endeavoring to assess that which may be encompassed. The disclosure of application S.N. 09/753350 is identical to that of application S.N. 09/752533. All VPM's that are disclosed in 09/753350 are also disclosed in 09/752533 and *vice versa*. All BPM's that are disclosed in 09/752533 are also disclosed in 09/753350 and *vice versa*. Claim 22 of 09/753350 does not mention the group $\text{-OCH}_2\text{-CH}_2\text{O-}$, but it is clear, just from a reading of claim 32 (even without the disclosure) that VPM's comprising PEG are encompassed. The two genera do not coincide exactly, but there is clearly substantial overlap of the claimed subject matter.

The claims are rendered obvious.



Claims 64, 78 and 80 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 46 of U.S. Serial No. 09/590,592; claim 68 is provisionally rejected as unpatentable over claim 54 of the '592 application. Although the conflicting claims are not identical, they are not

patentably distinct from each other.

Claim 46 of 09/590592 is drawn to a conjugate of a VPM and a BAM, wherein the VPM is specified to be that recited in claim 38 of 09/590592. The VPM recited in claim 38 of 09/590592 is not recited in 09/752,533; “two-way” obviousness is not being asserted by the examiner. However, the conjugates of 09/590592 have all of the structural features required by claim 64 of the instant application. Claim 54 of the ‘592 application recites that the “BAM” can be a polynucleotide, and so claim 68 of the instant application is rendered obvious thereby. [This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented].

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d)

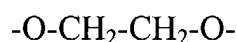


The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64, 66-77, 79, 83-97 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Descriptive support is lacking for the claimed invention. Consider first the requirement that the VPM must comprise the following functional group:



The response (filed 1/5/04) argues (on page 12 of the response) that support for this limitation can be found at various points on pages 9, 10, 12, and 20. However, nowhere on these pages (or any other pages) is there any suggestion that the VPM can comprise the functional group in question. Certainly, there are several references in the specification to PEG. However, the fact that a polymer of ethylene glycol is described does not constitute a basis for asserting that a monomer of ethylene glycol is described. As for claims 81 and 82, the passage on page 12, line 19 is noted, but this is for a molecule of formula 6 or 7. Perhaps it is true that claim 64 corresponds to a small subgenus of formula 6 or 7, but there is no reason given in the specification for selecting out the narrow subgenus of claim 64, with its recitation of ethylene glycol monomers and trimers.



Claims 81-82 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of claims 81 and 82 is dependent on a non-elected claim



The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 64, 68, 71 are rejected under 35 U.S.C. §103 as being unpatentable over Miyoshi (USP 4,820,812).

Miyoshi discloses and claims oligonucleotides bonded to sepharose. Also disclosed (col 9, line 45+) is epoxidized sepharose. Miyoshi does not describe the

oligonucleotides bonded to sepharose as valency platform molecule conjugates, and does not state that sepharose contains the following functional group: $\text{-O-CH}_2\text{-CH}_2\text{-O-}$

As is known to the chromatographic specialist of ordinary skill, agarose is a polysaccharide which contains alternating residues of D-galactose and 3-anhydrogalactose. Each of the anomeric carbon atoms has two oxygen atoms bonded thereto. Such an anomeric carbon, together with the atoms adjacent thereto, can be represented as follows: HO-CH-C(O)O

This structure comprises the following functional group: $\text{-O-CH}_2\text{-CH}_2\text{-O-}$

Accordingly, this particular limitation is met by the agarose. Sepharose is crosslinked agarose, and so the "branched" structure arises as a result. In addition, the requisite functional group arises in another way. As disclosed at col 9, line 55+ of the patent, a preferred chromatographic support is epoxidized sepharose. Upon reaction with a nucleophile, the epoxide opens, and the result is a structure which "comprises" the following: $\text{-O-CH}_2\text{-CH}_2\text{-O-}$

Thus, the limitations of the claims are met; the claims are rendered obvious by Miyoshi.



Claims 64, 67, 68, 78, 80, 83 are rejected under 35 U.S.C. §103 as being unpatentable over Tullis (USP 4904582) in view of Lehninger (pages 742-743).

Tullis discloses, throughout the patent, examples of polynucleotides bearing a polyethylene glycol group (abbreviated PEG) at the 5' position. Tullis does not describe this conjugate as branched; also not disclosed is that guanine, adenine, thymine and uracil are "biologically active" molecules.

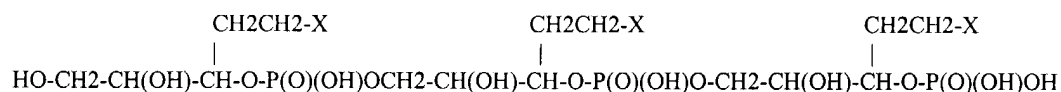
Lehninger discloses that guanine, adenine, thymine and uracil are "biologically active" molecules. Specifically, Lehninger discloses (page 742) that adenine is converted to adenosine monophosphate (AMP) by the action of phosphoribosyl transferase; guanine is similarly converted to guanosine monophosphate (GMP). Also disclosed (page 743) is that cytosine is converted to uracil by the action of cytosine deaminase, and that uracil is converted to dihydrouracil by the action of dihydrouracil dehydrogenase. Lehninger does not disclose branched molecules bearing a polyethylene glycol group, and at the same time, one or more guanine, adenine, thymine and uracil moieties.

The first issue concerns that of "branching". To begin with, consider the simple molecule 2-methylpentane. An organic chemist of ordinary skill would say that this is a "branched" molecule. Consider next the amino acid lysine. This also is a "branched" molecule; one can also say that lysine comprises two "branching groups". Consider next the following simple tetrapeptide:

Cys-Phe-Lys-Glu

This tetrapeptide is a branched molecule; it comprises at least four "branching groups".

It is noted that the tetrapeptide CFKE is not considered (by peptide chemists) to be a “branched peptide”, but the fact remains that it is a “branched” molecule. Consider next the following molecule, wherein “X” is a functional group (such as a halogen or a mesylate) that will facilitate bond formation between the carbon bearing “X”, and a nitrogen heterocycle:



This too is a “branched molecule”. If a bond is formed between each secondary alcohol and the (nearest) carbon bearing “X”, the result is a molecule which is a trimer of 2-deoxyribose-3-phosphate. This molecule is a “valency platform molecule” which is branched, and wherein the valency is at least three. In this molecule, the number of branching groups “pre-determines” the number of attachment sites for biologically active molecules. If the “biologically active molecules” are one or more of guanine, adenine, thymine and uracil, and if these “biologically active molecules” are bonded to the carbon bearing “X” (in the trimer of 2-deoxyribose-3-phosphate), the result is a deoxynucleoside triphosphate. The point of all this is simply that an oligonucleotide is really a “conjugate” between (a) a branched molecule that bears “attachment sites”,

and (b) biologically active molecules. The question of what “X” might be is not critical, since in the “conjugate”, “X” is not present. The molecule that contains “X” is a precursor of the molecule that is the subject of the claims. By the same token that “X” is not present, the “valency” referred to in claim 64 refers to a feature of a molecule which is not being claimed; the “valency” referred to in claim 64 refers to a feature of a precursor of the molecule that is the subject of the claims.

Consider again the fact that Tullis discloses a polynucleotide which bears a polyethylene glycol group at the 5’ position. This may be represented as follows:



wherein “Z” is PEG, “L” is a linking group between PEG and the polynucleotide, “Y” represents the last four nucleoside phosphates at the 5’ end of the polynucleotide, and “X” represents the polynucleotide, minus the last four nucleoside phosphates at the 5’ end. The “valency platform molecule” is then the group Y-L-Z, but without the nucleotide bases (guanine, adenine, thymine, uracil, etc.). The biologically active molecules are then the four nucleotide basis at the 5’ end, along with the polynucleotide fragment designated “X”.

Thus, the claims are rendered obvious.



Claims 64, 67, 68, 78 are rejected under 35 U.S.C. §103 as being unpatentable over

Greenwald (USP 5,567,422).

Greenwald discloses reaction of azlactone-derivatized PEG with various biologically active compounds such as proteins. In addition, conjugates of PEG and oligonucleotides are disclosed (col 9, lines 1-3). In a related vein, it is disclosed (col 4, line 52-58) that the subject azlactone-derivatized PEG will react with nucleotide bases such as guanine and adenine. Greenwald does not describe the PEG/oligonucleotide conjugates as being branched, and Greenwald does not disclose that ethanol is a "BAM".

One of ordinary skill would reason that the azlactone-derivatized PEG will react with nucleotide bases at various points along the structure of the oligonucleotide. The resulting structure will be branched. The "BAM's" in this case are (a) a 3'- or 5'-terminal fragment of the original oligonucleotide and (b) ethyl alcohol. With respect to the latter point, PEG is a polymer of recurring ethanol units (irrespective of how PEG may actually be synthesized). Thus, PEG contains "BAM's". With respect to claim 68, if an azlactone-derivatized PEG were to react, e.g., 10 nucleotide units from either the 3' end or the 5' end, the result would be a "branch" point at the point of bonding between the azlactone and the nucleophilic group on the nucleotide base. At the same time, there would be attached to this branch point a deca-nucleotide, thereby satisfying the requirements of claim 68.

Thus, the claims are rendered obvious.



Claims 64, 66, 67, 78, 80 are rejected under 35 U.S.C. §103 as being unpatentable over Sessler (USP 5,451,576).

Sessler discloses two compounds in figure 11C. Both of these compounds comprise PEG. Sessler does not disclose that ethyl alcohol is a “BAM”.

Though not stated in Sessler, it is well known to the pharmacologist of ordinary skill that ethanol is a “BAM”. Aside from its well-known effects on mental function, ethanol is an immunodepressant, a diuretic, an antimicrobial agent, and moreover ethanol affects various receptors including the NMDA receptor, the GABA receptor, and purinergic receptors.

The molecules depicted in figure 11C each comprise four molecules of ethanol. Two of them are bonded to the dimethoxyphenyl group, and the other two are bonded to the end of the PEG group; PEG is itself a polymer of ethyl alcohol. The valency of the molecule is four; the valency is determined not by reactive groups that are present in the claimed molecule, but rather by reactive groups that were present, or could have been present, prior to conjugation of the BAM's to the VPM.

Thus, the claims are rendered obvious.

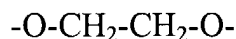


Claims 64, 67, 68, 70 are rejected under 35 U.S.C. §103 as being unpatentable over

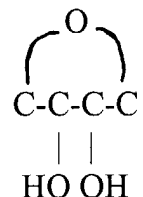
Datta, Bansidhar (*J. Biol. Chem.* **267**(7), 4497-502, 1992) or Osswald, Monika (*Nucleic Acids Research* **18**(23), 6755-60, 1990) or Doering, Thomas (*Nucleic Acids Research* **19**(13), 3517-24, 1991).

Each of the references (Datta, Osswald, Datta) discloses crosslinked RNA. In Datta, the proposed structure is depicted in figure 7 (p. 4502) of the reference. In Osswald, the proposed structure is depicted in figure 2; in Doering, the proposed structure is depicted in figure 4. None of the references describes the crossed-linked RNA as a conjugate between a VPM and a BAM.

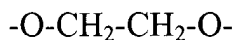
The first point concerns the requirement for the following functional group:



As is well known to the nucleic acid chemist of ordinary skill, RNA contains recurring pentose units, each of which comprises the following structure:



Thus, each pentose unit “comprises” the following functional group:



Claim 64 also requires branching. This requirement is met by the crosslinking that is disclosed in each of the references. Each crosslinked nucleotide base represents a

branch point. Thus, the RNA is fulfilling two roles: (a) a VPM which contains the following functional group: $-O-CH_2-CH_2-O-$, and (b) a "BAM".

Thus, the claims are rendered obvious.

✱

References 17, 19 and 21 were not considered because of the absence of a translation. However, the abstracts were considered.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton 6/1/04

Christopher S. F. Low
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